**OPHTHALMIC ARTERY DOPPLER ANALYSIS:
A WINDOW INTO THE CEREBROVASCULATURE OF WOMEN WITH PRE-ECLAMPSIA**

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ABSTRACT

The neurological complications of pre-eclampsia, including eclampsia (seizures) and intracerebral haemorrhage, are responsible for much of the maternal morbidity and mortality associated with this condition. Animal models and neuroimaging in humans suggest that pre-eclampsia is associated with a loss of cerebral autoregulation, which consequent hyperperfusion and vasogenic oedema. Treatments given to pre-eclamptic women are aimed at preventing these cerebral sequelae, and include antihypertensive agents (to prevent intracranial haemorrhage) and magnesium sulphate (for seizure prophylaxis). It is likely that these agents have a direct effect on the maternal cerebrovasculature, although their precise mechanisms of action remain incompletely understood.

Doppler analysis of the maternal ophthalmic artery represents a safe, well-tolerated, reproducible, readily accessible, real-time imaging modality by which cerebrovascular haemodynamic changes can be assessed. Existing research has shown pre-eclampsia to be associated with changes in the Doppler parameters of the ophthalmic artery that are consistent with increased perfusion. This sonographic technique could also be used to determine the cerebrovascular effects of anticonvulsant and antihypertensive therapies in pre-eclampsia. In time, it may prove to be a useful point-of-care tool for the individualisation of

risk for neurological events in pre-eclampsia, potentially allowing for more appropriately targeted therapy, and ensuring an adequate cerebrovascular response in those deemed high risk. In so doing, ophthalmic artery Doppler studies may play an important role in ameliorating the potentially devastating short- and long-term cerebral complications of pre-eclampsia.

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INTRODUCTION

Pre-eclampsia remains the commonest serious medical disorder of human pregnancy, complicating in the order of 3-4% of maternities worldwide.^{1,2} It is a leading cause of maternal mortality, with around 12% of such deaths being attributable to this condition and its complications.³ Neurological events, such as intracranial haemorrhage and eclampsia (the pathognomonic convulsive endpoint of pre-eclampsia), are some of the more frequent means by which pre-eclampsia kills mothers,⁴ along with hepatic rupture and acute pulmonary oedema. In addition to mortality, pre-eclampsia is associated with significant short and long-term maternal morbidity.⁵ Again, the neurological sequelae of this condition are responsible for a significant proportion of this morbidity,⁶ and include visual impairment, permanent neurological deficits after stroke, and cognitive impairment in later life.^{7,8}

The centrality of the placenta in the pathogenesis of pre-eclampsia is a widely-held and well-established concept in the literature,⁹ with the development of early-onset pre-eclampsia thought to be a two-stage process: deficient spiral artery remodelling, followed by placental oxidative stress in the context of inadequate perfusion,¹⁰ which results in a systemic inflammatory response that involves widespread endothelial dysfunction.¹¹ It has recently been proposed that later-onset pre-eclampsia, which is often not accompanied by fetal growth restriction¹² or overtly deficient placentation, may still be a product of placental oxidative stress caused by the 'microvillous overcrowding' that typifies a placenta unable meet fetal metabolic demands.¹³ Notwithstanding this central role of the placenta, pre-eclampsia is much

more than a purely 'placental' disease,¹⁴ not only in terms of its sequelae, but also with respect to the cardiovascular factors that may underpin the evolution of at least some phenotypes of this heterogeneous condition.¹⁵

To this end, there is an increasing awareness of the potential value of assessing maternal haemodynamics and vascular beds outside the uteroplacental unit,¹⁶ both as an alternative means of predicting pre-eclampsia, and as an adjunct to the assessment of women with established disease. The role of maternal echocardiography in this context is gaining traction, and research in this field has substantially enhanced our conceptualisation of the cardiac effects^{17,18} and potential causes¹⁹ of pre-eclampsia. Given the magnitude of the neurological effects of pre-eclampsia, research effort has also been expended on evaluating the cerebrovascular changes associated with this condition,²⁰ although real-time assessment thereof is challenging with established imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). This editorial appraises current knowledge of the utility of maternal ophthalmic artery Doppler interrogation as a tool to assess the cerebrovasculature in women with pre-eclampsia, and proposes potential future applications of this point-of-care imaging tool.

CEREBRAL COMPLICATIONS OF PRE-ECLAMPSIA: ASSESSMENT AND PREVENTION

As is the case for the condition overall, the precise pathophysiological mechanisms that underlie the neurological effects of pre-eclampsia remain to be determined.²¹ Research in this

field is constrained by the inability to correlate cerebral histopathology with functional imaging studies, as performance of one essentially renders performance of the other impossible.²⁰

Post-mortem studies have generally demonstrated gross intracranial haemorrhage, or small cortical petechial haemorrhages or infarcts.²² The primary neurological sequelae of pre-eclampsia, namely stroke, eclampsia and headache/visual disturbance, are likely to share common pathological origins related to cerebrovascular endothelial dysfunction in the context of impaired cerebral autoregulation as a consequence of systemic hypertension.

Two pathogenic pathways that explain the development of eclampsia have been proposed, based on different hypotheses regarding the cerebrovascular response to systemic hypertension, and varied associated findings on neuroimaging:

- Loss of cerebral autoregulation, leading to hyperperfusion, extracellular (vasogenic) oedema,²³ and thus the posterior reversible encephalopathy syndrome (PRES),²⁰ also known as reversible posterior leucoencephalopathy syndrome (RPLS),^{24,25} and
- Cerebral 'overregulation', leading to vasospasm, ischaemia and intracellular (cytotoxic) oedema.²⁶⁻²⁸

PRES is unique to neither eclampsia nor pregnancy, and is associated with a wide spectrum of hypertensive states, although it may take a less severe course in its gestational form.²⁹ There is evolving evidence that PRES is the pathognomonic lesion of eclampsia,^{30,31} and is commonly found in women with severe pre-eclampsia accompanied by neurological symptoms.³² On neuroimaging, PRES is denoted by symmetrical lesions of vasogenic oedema, predominantly in the parieto-occipital lobes.³³ The pressure from oedema may result in vasoconstriction, and

thus co-existent evidence of ischaemia/infarction.³⁴ The term PRES is a misnomer, given that it can affect any part of the brain, and is not universally reversible.³⁵

Although delivery of the fetoplacental unit is the only cure for pre-eclampsia, women remain at risk of its complications for some time afterward:³⁶ all nine Australian maternal deaths from pre-eclampsia in the most recent quinquennium occurred post-partum, seven of which were the result of intracranial haemorrhage.³⁷ Pharmacological therapies employed in pre-eclampsia are aimed at preventing these maternal neurological complications,³⁸ although none has been shown to alter the underlying course of the disease.

Neuroimaging in pre-eclampsia

Cerebrovascular changes in pre-eclampsia have been studied using transcranial Doppler (TCD) of the middle cerebral artery and other larger intracranial vessels (the skull precluding Doppler interrogation of smaller-calibre vasculature), computed tomography (CT) scanning, and magnetic resonance imaging (MRI). MRI studies have demonstrated increased cerebral blood flow in women with pre-eclampsia – an increase that is not a consequence of changes in the major vessels supplying the brain, as the diameter of these vessels does not change.³⁹ These observations support hyperperfusion as the underlying cause of cerebral injury in pre-eclampsia. TCD studies in pre-eclampsia have generally demonstrated increased velocities in large calibre cerebral vessels,^{40,41} increased flow indices (surrogate markers of volumetric flow),^{42,43} and increased cerebral perfusion pressures.⁴⁴⁻⁴⁷ A cohort study in 2013 employed

TCD to determine cerebral autoregulation among twenty women with untreated pre-eclampsia and twenty controls, and found *no* correlation between blood pressure or clinical features of disease and impaired cerebral autoregulation, despite the significantly reduced autoregulation index in the study group.⁴⁸ This potentially explains why the clinical prediction of eclampsia and intracerebral haemorrhage remains difficult.

Pharmacotherapy employed in pre-eclampsia

Antihypertensive agents are understood to prevent intracranial haemorrhage in pre-eclampsia by maintaining the mean arterial pressure within the range that does not compromise cerebral autoregulation, although the precise definition of this range may not be the same as in the non-pregnant population,^{49,50} and MAP alone may not be the only determinant of bleeding in this context.⁵¹ Methyldopa has been shown to reduce blood velocities in the middle cerebral arteries in pre-eclampsia,⁵² and labetalol reduces cerebral perfusion pressure without altering the cerebral flow index.⁵³ A recent study that evaluated the effects of methyldopa with or without nifedipine found that cerebral perfusion pressure remained elevated in pre-eclamptic women even when their blood pressures were controlled in line with target thresholds stipulated in clinical guidelines (systolic of < 140 mmHg),⁴⁷ highlighting the limitations of standard clinical assessments in establishing cerebrovascular risk.

The superiority of magnesium sulphate over other anticonvulsants in the prevention and treatment of eclampsia has been demonstrated in the Magpie (MAGnesium sulphate for

Prevention of Eclampsia) trial⁵⁴ and subsequent meta-analyses.⁵⁵ The mechanism of action of magnesium sulphate in preventing eclampsia is unclear, and may be multifactorial, with animal models providing support for a number of theories.⁵⁶ MRI studies have confirmed that magnesium sulphate does not affect the diameter of large-calibre intracranial vessels,⁵⁷ and so it may exert its effect on the cerebrovasculature by vasodilating smaller-calibre vessels,⁵⁸ or by reducing the cerebral perfusion pressure.^{59,60} Alternatively, or indeed additionally, it may elevate the seizure threshold through membrane stabilisation or other central effects.^{56,61} It has been proposed that antihypertensive therapy (such as labetalol) could be a more easily administered and less costly alternative to magnesium sulphate for eclampsia prophylaxis, given the likely role that compromised cerebral autoregulation plays in the pathogenesis of eclamptic seizures.⁶² Support for this theory arises from the low rates of eclampsia in centres that use antihypertensive therapy liberally and restrict use of magnesium sulphate, but although pilot trial data were promising,⁶³ it has proven challenging to conduct prospective randomised trials of labetalol for seizure prophylaxis in the post-Magpie era.

THE MATERNAL OPHTHALMIC ARTERY: A WINDOW INTO THE CEREBROVASULATURE

The methods for assessing the cerebral vasculature described above possess a number of limitations, including the risks of ionising radiation in the case of CT scanning, and significant logistical challenges in performing 'real time', longitudinal assessments of pre-eclamptic women with both CT and MRI investigations, which cannot be applied at the point of care, and remain relatively expensive. Transcranial Doppler studies can be performed in real-time, but

can only assess the large-calibre intracranial vessels such as the middle cerebral artery, which may not represent the level of the cerebrovasculature at which changes occur in pre-eclampsia and the treatment thereof.

Analysis of the spectral Doppler waveform of the maternal ophthalmic artery may provide an inexpensive, readily reproducible,⁶⁴ safe, non-invasive functional point-of-care imaging modality by which to assess the cerebral effects of pre-eclampsia and the impact of pharmacotherapeutic agents used in its management. Given the embryological, anatomical and functional similarities between the ophthalmic artery and the less accessible intracranial vasculature,^{65,66} cerebrovascular haemodynamics are thought to be directly reflected in this vessel's Doppler parameters. Ultrasonography of this artery is a well-established imaging modality, and has been utilised in the study of a variety of non-obstetric pathologies, including glaucoma,⁶⁷ heart failure,⁶⁸ systemic atherosclerosis,⁶⁹ and multiple sclerosis.⁷⁰ In the gynaecological context, it has been demonstrated that use of tibolone by healthy post-menopausal women does not alter the Doppler indices of this vessel.⁷¹ Ophthalmic Doppler sonography is well tolerated by patients, and does not take long to perform. Technical aspects of the examination technique⁷² are outlined in table 1, while figure 1 represents the duplex image thereby obtained.

<Table 1>

<Figure 1>

The ophthalmic artery Doppler spectral waveform

Figure 1 also demonstrates the time/velocity waveform generated by pulsed wave Doppler interrogation of the ophthalmic artery. It is characteristically dicrotic, in that it has a diastolic peak in addition to the systolic peak.⁷³ From this waveform, a number of standard indices can be calculated, including the pulsatility index (PI) and resistance index (RI). Although both are generally accepted to reflect downstream vascular resistance,⁷⁴ the former is more widely used than the latter because it incorporates the entire waveform by virtue of including the mean velocity in its calculation. The dicrotic pattern of this waveform permits calculation of a further index, the 'peak ratio': the ratio of the first diastolic peak to the peak systolic velocity.

Ophthalmic artery Doppler studies in healthy pregnancy

Reference ranges for Doppler parameters of the ophthalmic artery in healthy pregnancy have been established in a Canadian,⁷⁵ Japanese,⁷⁶ and four Brazilian populations: three from twenty weeks' gestation onwards,⁷⁷⁻⁷⁹ and one in the first trimester.⁸⁰ Most of these studies have shown that the resistance index (RI) and pulsatility index (PI) decline with advancing gestational age, but that the peak ratio (PR) does not change between 20 and 40 weeks' gestation, with de Oliveira et al⁷⁹ identifying a mean PR of 0.542 ± 0.097 (SD) in 289 healthy pregnant women, and Correa-Silva et al⁷⁸ finding a mean of 0.585 ± 0.16 (n = 63). As a consequence, and given that it reflects the specific features of the ophthalmic artery Doppler

waveform, the peak ratio has been proposed as the most sensitive parameter by which to assess changes in this vessel.^{73,77} It has been shown that measurements do not differ between the right and left eyes, validating unilateral assessment.⁷⁸

Ophthalmic artery Doppler studies in the prediction of pre-eclampsia

Ophthalmic artery Doppler parameters have been evaluated in both the first and second trimesters to determine their utility in predicting the later development of pre-eclampsia. In the first trimester, the ophthalmic artery PI performs as well as the uterine artery PI in multiparametric predictive models for pre-eclampsia, indicating that – even in early pregnancy – cerebrovascular changes may be occurring in those destined to develop the disease.⁸¹

Although the clinical utility of this approach is likely to be limited, given that the uterine arteries can more readily be assessed at the time of the 12-week nuchal translucency scan, it may be of value in women whose uterine circulation cannot be adequately interrogated by Doppler sonography, such as the morbidly obese.

In the mid-trimester, among women at high risk of hypertensive complications of pregnancy, an elevated 'peak mesodiastolic velocity' (first diastolic peak velocity) has been shown to be an independent predictor for pre-eclampsia in the third trimester.⁸² The same authors had earlier shown all ophthalmic artery Doppler velocities and indices to be increased when assessed in the second trimester in women who went on to develop pre-eclampsia.⁸³ However, a recent prospective observational cohort study found that ophthalmic artery Doppler analysis added

little to the predictive utility of a combination of maternal characteristics and uterine artery PI in the mid-trimester,⁸⁴ and as a consequence, its clinical value in this context is likely to be limited.

Ophthalmic artery Doppler studies in pre-eclamptic pregnancy

Numerous studies have evaluated changes in ophthalmic artery Doppler parameters in women with pre-eclampsia, results of which are summarised in table 2. Among women with pre-eclampsia, these studies have generally shown decreased resistance and pulsatility indices combined with increased blood flow velocity and peak ratios, suggesting decreased vascular resistance. The largest study that reported all relevant Doppler parameters⁸⁵ found a mean resistance index, pulsatility index and peak ratio in thirty women with severe pre-eclampsia of 0.63 ± 0.09 , 1.13 ± 0.31 , and 0.89 ± 0.12 respectively, as against means of 0.75 ± 0.05 , 1.88 ± 0.43 , and 0.52 ± 0.1 in 289 healthy controls. Overall, however, these studies involved only small numbers of patients, and some included patients with both treated and untreated pre-eclampsia in the populations studied, leading to significant heterogeneity in the results.

<Table 2>

After delivery, the changes in the ophthalmic artery Doppler parameters of pre-eclamptic women may take some time to resolve, with a recent study demonstrating persistent differences up to three months post-partum in comparison to women with normotensive

pregnancies.⁸⁶ This serves to reinforce our evolving understanding that many features of pre-eclampsia may take much longer than the conventional six weeks to resolve.⁸⁷

Very little research has been conducted into the effects of pharmacotherapy used in pre-eclampsia on the Doppler parameters of the ophthalmic artery. Nakatsuka et al.⁸⁸ assessed the impact of transdermal isosorbide dinitrate (a nitric oxide donor antihypertensive) in pre-eclamptic women, and found that the drug lowered the end diastolic velocity and peak ratio of the ophthalmic artery, whereas other indices were unchanged. In an earlier study, Belfort⁸⁹ evaluated the effect of intravenous magnesium sulphate administration on the Doppler parameters of the ophthalmic, posterior ciliary and central retinal arteries in patients with pre-eclampsia, but only reported the results for the latter two vessels, with both demonstrating a reduction in pulsatility index after the drug was given. The same group had previously published similar findings on the effect of magnesium sulphate on these ocular vessels,^{58,90} and evaluated Doppler changes in the central retinal artery following administration of nimodipine to an eclamptic patient, which similarly resulted in a reduction in the pulsatility index.⁹¹

The effects of antihypertensives commonly used in pre-eclampsia, such as nifedipine, hydralazine, methyldopa and labetalol, or those of magnesium sulphate, on the Doppler parameters of the ophthalmic artery do not appear to have been reported in the literature to date.

Limitations of velocimetry

The Doppler parameters reported above are all *velocimetric* in nature: measurements of blood *velocity* at various points of the cardiac cycle, and indices derived from these velocities. It is important to recognise that such parameters are *not* measurements of *volumetric* blood flow,¹⁶ assessment of which must take into consideration the calibre of the vessel, changes in vessel calibre along its length, changes in velocity over the cardiac cycle, and the angle at which the interrogation is performed (which should be less than 20°).⁹² The relatively tortuous nature of the ophthalmic artery renders accurate assessment of its calibre along its length difficult to achieve, generally limiting the capacity for Doppler ultrasound to assess volumetric flow therein. This limitation must be borne in mind when interpreting velocimetric parameters,⁹³ although they have been shown to reflect accurately aspects of volumetric flow in other cerebral vessels.⁹⁴ Additionally, Doppler velocimetric parameters have been well validated as clinical tests in other areas, such as the use of umbilical artery pulsatility index in the assessment of the growth-restricted fetus.⁹⁵

FUTURE APPLICATIONS OF MATERNAL OPHTHALMIC ARTERY DOPPLER ANALYSIS

Intracranial haemorrhage and eclampsia remain rare but potentially catastrophic complications of pre-eclampsia. Even among women with 'severe' disease,⁹⁶ it is difficult to predict who is at significant risk of these complications. As noted earlier, mean arterial pressure may not be adequate for this purpose,^{48,51} and substantial numbers of women need to receive magnesium sulphate to prevent one case of eclampsia (number-needed-to-treat

[NNT] of 63 for women with severe pre-eclampsia, and 109 for those with mild disease).⁵⁴

Most women with severe pre-eclampsia will not progress to eclampsia or stroke, but some patients with hitherto apparently clinically mild disease will suffer these complications, highlighting the need for individualised risk prediction strategies that would permit a more targeted application of anticonvulsant and antihypertensive therapy than current commonly employed indications, such as 'severe hypertension' or 'neurological excitability'. Such strategies could also have significant health economic benefits, if they could safely reduce the NNTs of these therapies.

In addition to providing real-time insights into maternal cerebrovascular parameters in pre-eclampsia, and the changes induced therein by anticonvulsant and antihypertensive therapies, ophthalmic artery Doppler analysis may prove to be a readily applicable tool by which a patient's specific risk for cerebral complications may be estimated with greater precision than is currently possible. This may prevent unnecessary treatment, with its associated costs and adverse effects, and could ensure an adequate response to therapy in those patients whose abnormal Doppler parameters render them high risk. Such targeted therapy may also prove to be beneficial in reducing the long-term maternal health risks associated with pre-eclampsia.⁵

The substantial heterogeneity of extant studies necessitates further adequately powered prospective research across a range of populations to evaluate the potential utility of this point-of-care sonographic technique.

CONCLUSIONS

Although effective therapies exist to mitigate the maternal cerebral complications of pre-eclampsia, their mechanism of action remains incompletely understood, and clinical assessment of *who* needs *how much* of such treatments is currently based on imprecise measures. CT and MRI brain imaging is expensive, and cannot be applied in real-time at the bedside. The anatomical and functional similarities between the accessible ophthalmic artery and inaccessible smaller calibre cerebral vessels have led to Doppler interrogation of the former being applied to investigate changes in the haemodynamics of the latter. This safe, reproducible, point-of-care examination has demonstrated Doppler indices in pre-eclamptic women that are consistent with cerebral hyperperfusion. It may prove to be a useful research tool to determine the cerebrovascular mechanisms of action of anticonvulsant and antihypertensive therapies used in pre-eclampsia, with potential clinical application in the refinement of individual risk for neurological complications, and assessment of therapeutic response in those deemed to be at high risk.

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DISCLOSURE OF INTERESTS

The authors have no competing or conflicting interests to declare.

ETHICS APPROVAL

Institutional ethics review board approval was not required for the preparation of this editorial. Signed consent was obtained from the patients whose sonographic examinations produced the images included in this manuscript.

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FIGURE LEGENDS

Figure 1: B-mode image of the orbit and retro-orbital structures, with superimposed colour Doppler for the identification of the ophthalmic artery and pulsed wave Doppler to acquire its spectral waveform. The typical spectral waveform is shown below. PSV = peak systolic velocity, FDP = first diastolic peak velocity, EDV = end diastolic velocity.

TABLE 1: Technique for Doppler interrogation of the ophthalmic artery⁷²

- A linear array transducer is used, with a frequency between 7 and 15 MHz
- The transducer is applied directly to the closed eyelid following application of a drop of gel
- The transducer is positioned horizontally over the upper aspect of the eyeball
- Using colour Doppler, the ophthalmic artery is identified by its direction of flow (toward the probe) and pulsatility
- Pulsed wave Doppler is then applied, with the sample volume placed around 15 mm behind the optic disc, medial to the optic nerve; the sample volume should be 2 mm in length
- Three to five consistent cardiac cycles are obtained and stored electronically
- The insonation angle is kept at less than 20°, with the high-pass filter set to its minimum value
- The PRF (pulse repetition frequency) should be set at 125 kHz, and adapted as necessary.

TABLE 2: Studies of Doppler parameters of the maternal ophthalmic artery in pre-eclamptic pregnancy (adapted from Matias et al. 2012,⁷³ reproduced with permission)

Study	Study Design	Variables	Comparison Groups	Pre-eclampsia
Hata et al. 1992 ⁹⁷	Cross-sectional	PSV, EDV, MV, PI	NP × HP × PE	Lower PI
Hata et al. 1995 ⁹⁸	Cross-sectional	PSV, EDV, MV, PI	HP × PE	Higher velocities, lower PI
Giannina et al. 1997 ⁹⁹	Cross-sectional	PSV, EDV, MV, RI, PI	HP × PE	Higher velocities, lower RI and PI
Hata et al. 1997 ¹⁰⁰	Cross-sectional	PSV, EDV, MV, PI	NP × HP × PE × GH × CH	Lower PI in severe pre-eclampsia
Belfort et al. 1999 ¹⁰¹	Cross-sectional	PSV, EDV, MV, RI	NP × PE	Lower RI, increases as MAP increases
Ohno et al. 1999 ⁷⁶	Cross-sectional	PSV, EDV, MV, PI	HP × PE	Lower PI when eclampsia is imminent
Takata et al. 2002 ¹⁰²	Cross-sectional	PSV, EDV, MV, RI, PI, PR	HP × IUGR × PE	Higher PR
Ayaz et al. 2003 ¹⁰³	Cross-sectional	PSV, EDV, PI, RI	HP × PE	Lower RI and PI; ↑ if worsening PE
Diniz et al. 2008 ¹⁰⁴	Cross-sectional	PSV, PDV, RI, PI, PR	HP × PE	Higher velocities and PR; ↑ with worsening PE
Barbosa et al. 2010 ¹⁰⁵	Longitudinal	RI	Severe PE	RI lower than 0.56
De Oliveira et al. 2013 ⁸⁵	Cross-sectional	RI, PI, PR	CH × PE (mild) × PE (severe) × HP	Lower RI and PI, higher PR
Paes et al. 2014 ¹⁰⁶	Cross-sectional	PSV, PDV, RI, PI, PR	HP × mild PE × severe PE × pregnant	Lower RI and PI, higher PR

			smokers	
<p><i>Abbreviations: GH, gestational hypertension; HP, healthy pregnancies; IUGR, intrauterine growth restriction; MAP, mean arterial pressure; NP, not pregnant; PDV, peak diastolic velocity; PI, pulsatility index; PR, peak ratio; PSV, peak systolic velocity; RI, resistance index; PE, preeclampsia.</i></p>

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